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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Gary E. Parker
ZymoGenetics, Inc.
1201 Eastlake Avenue East
Seattle, WA 98102

EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 06/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/695,121	GILBERTSON, DEBRA G.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,9,11-13,15 and 17-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,9,11-13,15 and 17-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 October 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Prosecution on the merits of this application is reopened on claims 1-6, 9, 11-13, 15 and 17-25. Prosecution is reopened in view of the rejections indicated herein.

2. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1-6, 9, 11-13, 15 and 17-25 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 41, 42, and 46-54 of copending Application No. 10/139,583 ('583, herafter). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of '583 are drawn to methods of inhibiting zvegf3 activity in a mammal by administering a zvegf3 antagonist (claim 41), such as an antibody or antibody (claim 42), and methods of decreasing zvegf3 activity in a mammal by administering an antibody specific for an epitope of zvegf3 (claims 46, 50) wherein the antibody can be a monoclonal antibody (claim 47, 51), a humanized

antibody (claim 48, 52) or a single chain antibody (claim 49, 54). The antibodies used in claims 46-54 of '583 are specific for the same epitopes of zvegf3 as the antibody used in the methods of the instant application.

NOTE: This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented, and this provisional rejection is appropriate considering the claims are not allowable in view of the rejections indicated below.

Claim Rejections - 35 USC § 112, first paragraph

1. Claims 11-13, 15, 24 and 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

2. A method for reducing fibrosis caused by zvegf3 activity in a mammal comprising administering to the mammal a composition comprising a zvegf3 antagonist in combination with a pharmaceutically acceptable delivery vehicle, in an amount sufficient to reduce zvegf3 activity, wherein said zvegf3 antagonist is an antibody that specifically binds to a dimeric protein having two polypeptide chains, wherein each of the polypeptide chains consists of a sequence of amino acid residues selected from the group set forth (see claim 1);

does not reasonably provide enablement for the full scope of the claims. Specifically, the claims are not enabled for **treating** fibrosis caused by zvegf3 to the extent that treating encompasses completely eliminating and preventing any future occurrence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to methods of treating fibrosis in a mammal using a zvegf3 antagonist wherein said zvegf3 antagonist is an antibody. The specification indicates that overexpression of Zvegf3 leads to stellate cell activation, extracellular matrix growth and increased cell proliferation (see p. 10, lines 12-20).

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to methods of treating fibrosis in a mammal using a zvegf3 antagonist wherein said zvegf3 antagonist is an antibody that specifically binds to a dimeric protein having two polypeptide chains wherein each of said polypeptide chains consists of a sequence of amino acid residues present in zvegf3 (specifically in the region of residues 230-345 of SEQ ID NO 2). The claims encompass methods treating and preventing symptoms associated with mammalian disease or disorder using an antibody. Therefore, the nature of the invention using an antibody to treat or prevent a mammalian disorder.

The breadth of the claims

The claims encompass treating fibrosis (caused by zvegf3) in a mammal, which encompasses completely eliminating and preventing any future occurrence of fibrosis caused by zvegf3 in the mammal. It is noted that specification indicates that the claims encompass reducing cell proliferation associated with cancer (prostate carcinoma, see p.12 lines 27-34 of the specification), hepatitis, scleroderma, **liver fibrosis**, etc. (p. 10, lines34-p. 11 line 10)), treating fibrosis associated with diabetes, (p. 11, lines 21-35), pneumonia, hypertension, etc. (p. 12, lines 12-20) and reducing stellate activation associated with fibrotic disorders of the liver (see p. 11 lines 17-20). Therefore, the claims encompass a method for treating and preventing fibrosis in a mammal.

The unpredictability of the art and the state of the prior art

With respect to the instant claims considering that "treatment" encompasses completely eliminating and preventing any future occurrence of fibrosis using an antibody specific for zvegf3, it is noted that the prior art does not recognize any antibody treatment that can completely eliminate and/or completely prevent any mammalian disorder. Regarding the "treatment" of renal diseases, Yu (Current Opin. Pharm. 2002; 2:177-181) teaches that angiostatin II blockade is a standard anti-fibrotic therapy for renal diseases, but also indicates that it is unlikely that any single agent will effectively stop renal fibrosis. Specifically, Yu teaches,

> "Angiostatin II blockade has become a standard anti-fibrotic therapy in renal diseases because it slows progression to end-stage renal disease. However, current data support the notion that angiotensin II blockade alone cannot stop progressive fibrotic disease. Of an increasing number of therapies showing efficacy in animal studies, antibodies to transforming growth factor beta are the most thoroughly studied and are likely to be effective in human clinical trials. However, hints exist in the literature suggesting that no

single agent will effectively halt renal fibrosis and that combinations of agents will be required." (See abstract, emphasis added).

Therefore, it is unlikely that that administration of zvegf3 antibody would be able to completely eliminate and/or prevent fibrosis in a mammal, without evidence to the contrary.

Working Examples and Guidance in the Specification

As mentioned in the previous Office Action, the specification has no working examples, whatsoever, demonstrating administration of a zvegf3 antibody to a mammal. There is no demonstration that administration of the zvegf3 antibodies can effectively "treat" (i.e., completely eliminate and prevent any future occurrence) fibrosis in a mammal. The specification does indicate that overexpression of Zvegf3 leads to increased cell proliferation, increased extracellular matrix formation and stimulates production of TGF-B1 in stellate cells (an indication of stellate cell activation). However, the claims are very broad and encompass "treating" fibrosis by administration of a Zvegf3 antibody. Considering the relevant art does not recognize that an antibody can be used to completely eliminate and/or completely prevent any mammalian disorder, one of skill in the art could not predict that Zvegf3 antibody treatment would effectively "treat" fibrosis caused by zvegf3 in a mammal without performing additional experimentation to show that the zvegf3 antibody could completely eliminate and prevent any future occurrence of fibrosis in the mammal.

Quantity of Experimentation

Considering there is no indication in the prior art that antibodies can be used to completely eliminate and/or prevent any mammalian disorder, one of skill in the art could not

reasonably predict that the zvegf3 antibody could be used to "treat" fibrosis caused by zvegf3 without specific supporting evidence. The amount of additional experimentation required is considered to be undue because it would have to be shown that zvegf3 antibody could be used to completely eliminate and prevent fibrosis with a reasonable expectation of success.

Level of the skill in the art

The level of the skill required is deemed to be high, considering the highly technical nature of the field.

Conclusion

Considering the high degree of unpredictability recognized in the art, the breadth of the claims, the lack of working examples and guidance in the specification; and the high degree of skill required, it is concluded that the amount of experimentation required to use the claimed invention to the full scope encompassed by the broad claims is undue.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an

international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

6. Claims 1-6, 9, 11-13, 15 and 17-25 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent 6,455,283 (Ferrara et al.).

7. The instant claims are drawn to methods for reducing cell proliferation or extracellular matrix production (as well as treating fibrosis and reducing stellate cell activation) caused by zvegf3 by administering an antibody that specifically binds to a dimeric **protein having** two polypeptide chains, wherein each chain consists of amino acids 230-345 of SEQ ID NO: 2 (or amino acids 231-345, 232-345... 240-345 of SEQ ID NO: 2) wherein administration of the antibody results in reduction of proliferation or extracellular matrix production (as well as treating fibrosis and reducing stellate cell activation) caused by zvegf3 (emphasis added). It is noted that, as written, the claims are not limited to administering an antibody that specifically binds to a dimeric **protein consisting of** two polypeptide chains, wherein each chain consists of specific amino acids. As such, the claim encompass administering an antibody that specifically binds to a dimeric **protein having** (i.e., a dimeric protein that has at least) two polypeptide chains, wherein each chain consists of amino acids—including a dimeric protein having two polypeptide chains, each consisting of the full length amino acid sequence of SEQ ID NO: 2. It is noted, however, that limiting the claim to administering an antibody that specifically binds to a dimeric **protein consisting of** two polypeptide chains, wherein each chain consists of specific amino acids would not obviate this rejection, for the reasons indicated below.

8. It is noted that zvegf3 is identical in amino acid sequence to VEGF-E. Ferrara teaches a polypeptide, VEGF-E, which has the exact amino acid sequence of SEQ ID NO: 2, and thus comprises residues 230-345 of SEQ ID N0: 2 of the instant application with 100% sequence identity. Ferrara also teaches anti-VEGF-E antibodies, including polyclonal, monoclonal, humanized antibodies (column 54, line 12 to column 57, line 9), and methods of treatment using the antibody by administering the antibody to a mammal (column 60, line 63 to column 62, line 40). Ferrara specifically teaches that VEGF-E antagonists (such as antibodies specific for VEGF-E) are useful for "treatment of disorders where it is desired to limit or prevent angiogenesis." (See column 42 lines 58-60). Ferrara teaches, "Examples of such disorders include...scar tissue overproduction, for example, that seen in a keloid that forms after surgery, fibrosis after myocardial infarction, or fibrotic lesions associated with pulmonary fibrosis." (See paragraph bridging columns 42 and 43). Furthermore, Ferrara also teaches,

> "A VEGF-E polypeptide herein or antagonist thereto may also be useful for gut protection or regeneration and treatment of lung or **liver fibrosis**, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage. Also, the VEGF-E polypeptide or antagonist thereto may be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells, or for **inhibiting the growth of tissues described above**." (See column 45 lines 8-14, emphasis added).

9. Ferrara's anti-VEGF-E antibodies anticipate the antibodies to the polypeptide of SEQ ID NO: 2 (as well as the claimed fragments) as the amino acid sequences of zvegf3 and the zvegf3 fragments are encompassed by Ferrara's VEGF-E, as they share 100% sequence identity. It is noted that producing antibodies to the full-length zvegf3/VEGF-E protein would necessarily result in antibodies that are specific for the claimed zvegf3 fragments and dimeric proteins of said fragments. As such, Ferrara's method of treatment using the antibody would inherently

decrease zveg3 activity in a mammal. With respect to zvegf3 antibodies that specifically bind to a dimeric protein having two polypeptide chains of amino acids 230-345 through 240-345 of SEQ ID NO: 2 (e.g., see claim 1), although the reference does not explicitly mention an antibody to a homodimeric protein of VEGF-E, in the homodimeric protein comprises two polypeptides each of which can comprise a specific portion of zvegf3/VEGF-E. Therefore, the antibody of the prior art would necessarily bind to the dimeric protein of the present claims, absent evidence to the contrary. Furthermore, Ferrara specifically teaches that VEGF-E/zvegf3 antagonists (note: Ferrara specifically teaches VEGF-E/zvegf3 antibody is a VEGF-E/zvegf3 antagonist) are useful for treating liver fibrosis, as well as inhibiting the growth of tissues including liver and kidney tissue (See column 45, lines 8-14). It is noted that specification indicates that the claims encompass reducing cell proliferation associated with cancer (prostate carcinoma, see p.12 lines 27-34 of the specification), hepatitis, scleroderma, **liver fibrosis**, etc. (p. 10, lines34-p. 11 line 10)), treating fibrosis associated with diabetes, (p. 11, lines 21-35), pneumonia, hypertension, etc. (p. 12, lines 12-20) and reducing stellate activation associated with fibrotic disorders of the liver (see p. 11 lines 17-20). Therefore, the reference anticipates the instant claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (571) 272-0756. The examiner can normally be reached on M-F (8:00-5:30) with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon Eric Angell, Ph.D.
Art Unit 1635

DAVE T. NGUYEN
PRIMARY EXAMINER